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TREATMENT OF GONORRHOEA WITH P.A.M. AND PROBENECID*

BY

A. L. HILTON

From The Royal Infirmary, Doncaster

The relative resistance of gonococci to penicillin in certain areas in Britain has been thoroughly described by King (1958), Curtis and Wilkinson (1958), Cradock-Watson, Shooter, and Nicol (1958), and Willcox (1959). The last author and his colleagues at St. Mary's Hospital, London, had a failure rate of 17·9 per cent. using 1·2 mega units procaine penicillin G in oil with 2 per cent. aluminium monostearate (P.A.M.).

In 1958, at the Doncaster Royal Infirmary V.D. clinic, 39·3 per cent. of the male patients, who received 300,000 units P.A.M., had a persistent or only slightly reduced urethral discharge containing gonococci. Consequently a higher dose schedule was sought.

Curtis and Wilkinson have suggested that it would be worthwhile to devise a preparation of penicillin which would give a blood concentration of not less than 1 unit per ml. for at least 24 hrs. Probenecid (p (di-n-propylsulphamyl) benzoic acid) retards the loss of penicillin from the kidney tubules (Walker and Hunter, 1951), and has been given with oral penicillin for the treatment of gonorrhoea (Jacoby, Pollock, and Boghosian, 1954; Marmell and Prigot, 1957).

It was therefore decided to combine oral probenecid with P.A.M. given intramuscularly. After some preliminary work it was found that 1·2 mega units P.A.M. with probenecid 0·5 g. 6-hrly for 24 hrs gave a blood concentration approaching 1 unit per ml. 24 hrs after the single injection. The treatment was completely effective and confirmed the work of Curtis and Wilkinson (1958). Tests to discover the minimal concentrations of penicillin required to inhibit the growth of gonococci were carried out on nearly all the isolated strains. Serum penicillin levels were estimated as frequently as possible.

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Methods

In all patients included in the series the diagnosis was confirmed by culture. Sensitivity tests were carried out using penicillin-impregnated disks of the following strengths: 0·5, 0·25, 0·06, 0·015 unit/ml. penicillin.

Preliminary work (see Table I), measuring the penicillin serum level, 24 hrs after intramuscular P.A.M. alone and then after P.A.M. combined with oral probenecid, indicated that 1·2 mega units P.A.M. and 2 g. probenecid produced the desired concentration. Every patient therefore received this treatment.

TABLE I

SERUM PENICILLIN LEVELS AFTER INTRAMUSCULAR INJECTION OF P.A.M. ALONE AND P.A.M. WITH ORAL PROBENECID

Dose of P.A.M.	Dose of Oral Probenecid	Serum Penicillin Levels (units/ml.) after		
		21 Hours	23 Hours	24 Hours
600,000 units	—			0·1
				0·6
			0·1	
				0·2
			0·1	
	2 g.			0·4
				0·6
				0·6
				0·3
				0·5
				0·4
				0·4
		0·7		

One 0·5 g. tablet of the penicillin-retarding agent was given in the clinic and three more were provided to be taken at 6-hrly intervals. Strict instructions were issued and the following day the patients were questioned about the number of tablets taken and any possible toxic effects.

Their clinical state was noted and further smears and cultures were taken when these seemed to be required. At the same time blood was taken for serum penicillin assays. These were carried out by serial dilutions in Fleming's medium with an indicator incorporated, which were inoculated with the Oxford staphylococcus. The results were corroborated by using nutrient broth and subculturing the organism. It is possible that delay in the clinic and laboratory resulted in lower readings than would have been obtained by more speedy dispatch.

Results

The results of treating 64 patients are shown in Table II. There were no apparent failures, and the urethral discharge cleared within 48 hrs.

Re-infection.—One Irishman re-attended with a re-infection 35 days after his injection.

Two Jamaicans were re-infected twice and one Jamaican three times. Two of these men had regular consorts, one of whom was later persuaded to attend for treatment. Fresh exposures to risk were admitted by those who were re-infected and a purulent urethral discharge occurred 2 to 5 days later. When adequate follow-up was obtained the identical treatment was seen to be effective.

Co-existent Non-Gonococcal Urethritis.—Eleven male patients and all the female patients were subsequently screened with smears and cultures; five were taken to be cases of co-existing non-gonococcal urethritis and treated as such.

Side-Effects.—Two men (3·9 per cent. of the total number of males) complained of nausea after swallowing a tablet. A rash developed in one of these men, which was presumably due to the probenecid, as he failed to react to a skin-test with P.A.M. and 1 per cent. procaine. Four women (30·8 per cent. of the total number of females) complained of burning and soreness of the throat which lasted in one case for 2 days. One male patient had a generalized penicillin sensitivity eruption, the irritation being most marked at the site of injection.

All but one patient confirmed that all four tablets were ingested. The time spent on emphasizing the importance of remembering the tablets appeared to be worthwhile.

Sensitivity Tests.—The tests of penicillin sensitivity *in vitro* were a useful guide to the number of cases that would probably have relapsed on a lower penicillin schedule. However, the disk method was not thought sufficiently accurate to report in detail. The minimal concentration of penicillin required to inhibit the majority of strains was 0·25 unit/ml. penicillin.

Serum Penicillin Levels.—Serum penicillin estimations were carried out 21 to 30 hrs after injection in 48 patients (Table III). The levels ranged between 0·15 and 4·8 units/ml. penicillin (mean 1·27 units/ml.). In 81·3 per cent. of the series, the levels varied between 0·7 and 2·4 units/ml. penicillin.

TABLE III

SERUM PENICILLIN LEVELS 21 TO 30 HOURS AFTER ONE INJECTION OF 1·2 MEGA UNITS P.A.M. AND 0·5 G. ORAL PROBENECID 6-HRLY FOR 24 HRS

Hours after Injection and Tablets	Number of Patients	Serum Levels (units/ml.)		Number of Patients with Serum Levels between 0·7 and 2·4 units/ml.
		Range	Mean	
21 to 30	48	0·15 to 4·8	1·27	39

Discussion

Satisfactory results have been obtained in the treatment of acute gonorrhoea with 1·2 mega units P.A.M. and probenecid 0·5 g. 6-hrly for 24 hrs. A surprisingly large number of patients co-operated fully; this may have been due, at least in males, to the fact that when the last tablet was taken, 18 hrs after the visit to the clinic, the patient was still aware of his condition and anxious to get better. Side-effects were especially noticeable in women who were "never good at swallowing tablets". Perhaps if the tablets were crushed and taken in milk fewer patients would complain.

TABLE II

RESULT OF TREATING 64 PATIENTS WITH ACUTE GONORRHOEA WITH P.A.M. AND PROBENECID

Race	Sex	Treatment	No. of Cases Treated	No. of Cases Followed for 7 to 70 days	Non-Gonococcal Urethritis	Re-infections	Failures
White ..	Male ..	P.A.M. 1·2 mega units plus Probenecid 2 g.	34	31	4	1	—
	Female ..		13	12	—	—	—
Coloured	Male ..		17	15	1	7	—
Total			64	58	5	8	—

Attention should be drawn to the fact that a few patients had high penicillin serum levels. Kidney tubular function returns to normal within 24 hrs of stopping probenecid (Walker and Hunter, 1952), but extra care should be taken in preventing possible penicillin sensitivity reactions. One which occurred in this series was not severe.

The cost of the treatment was 3*s*. 4*d*., which compares well with that of 2 g. Chloramphenicol (7*s*.) or Terramycin (10*s*. 4*d*.), but unfavourably with that of 1 g. Streptomycin (1*s*. 2*d*.). If the gonococcus eventually develops complete resistance to the preparations of penicillin now available, preparations of the recently isolated 6-amino-penicillanic acid (*Lancet*, 1959) may prove effective.

Summary

A pilot study has been carried out in one particular area using 1·2 mega units P.A.M. and 0·5 g. oral Probenecid 6-hrly for 24 hrs in the treatment of acute gonorrhoea in white and coloured patients. There were no apparent failures in the series.

A mean serum penicillin level of 1·27 units/ml. was attained 21 to 30 hrs after the injection.

Co-operation of the patient, side-effects, and the expense of the treatment are discussed.

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ADDENDUM

Since this paper was written, the results as indicated above have been reproduced in 57 new male patients, but there have been failures in two out of a further eighteen female patients.